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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/658,688	**Applicant(s)** HERMANSON, GARY G.	
	Examiner Anoop Singh	**Art Unit** 1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 04 April 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: *231-244, 261-274*.
   Claim(s) rejected: *215-292*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER

Continuation of 5. Applicant's reply has overcome the following rejection(s): Applicant's reply has overcome in part the rejection pertaining to 35. US.C. 112, paragraph 1 and as discussed in continuation sheet..

11. The request for reconsideration has been considered but does NOT place the application in condition for allowance because: The amendments to claims 231 and 261 and arguments are not fully persuasive to overcome all the outstanding rejections of the record.

The Examiner maintains the rejection of claims 215-292 for the reasons as stated in previous office action. Claims 215-292 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to reduce the severity of anthrax infection in a mammal comprising: administering to a mammal a composition comprising a carrier, (+)-N- (3-aminopropyl)-N,N-dimethyl-2,3-bis(syn-9-tetradecenyloxy)-l-propanaminium bromide (GAP-DMORIE), a co-lipid selected from the list consisting of 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine (DPyPE), and 1,2-dimyristoyl-glycer-3-phosphoethanolamine(DMPE) and an isolated polynucleotide comprising a nucleic acid fragment which encodes a polypeptide at least 97% identical to amino acids 199 to 764 of SEQ ID NO:4, wherein said nucleic acid is ligated to a heterologous nucleic acid; wherein said heterologous nucleic acid encodes a heterologous polypeptide comprising human tissue plasminogen activator (hTPA) signal peptide fused to the polypeptide encoded by said nucleic acid fragment;

wherein said composition elicits an immune response to said polypeptide; and wherein said nucleic acid fragment is a variant fragment of an optimized coding region for the polypeptide of SEQ ID NO: as set forth in claim 215; does not reasonably provide enablement for a method of preventing anthrax.

It is noted that applicants have amended claims 231 and 261 to recite, "reduce severity of anthrax infection". Therefore, argument pertaining to a method to treat anthrax infection by administering the composition of the invention is moot in view of amendment to these claims. The argument presented in this advisory action is directed to a method to prevent anthrax infection and to the extent; claims embrace a carrier comprising GAP-DMORIE and any co lipid adminstered via ay route to elicit immune response.

Applicants argue that the terms "treatment or prevention" in the captioned application consistent with the art recognized use of these terms. The ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention. Applicants assert that it has provided claim definitions for the terms "treatment or prevention" in the captioned application. Specifically, the specification defines the term to prevent or treat, i.e. cure, ameliorate, lessen the severity of, or prevent or reduce contagion of infectious disease caused by *B. anthracis*. (See specification, paragraph [0057].) Therefore, the term encompasses a range of outcomes from lessening the severity of the disease to the prevention of infection. Applicants cite dictionary definition of "preventative" is "to come before, prevent," which is synonymous with prevention.

In response, it is noted that applicant agree that specification provides definitions for the terms "treatment or prevention" in the captioned application. Specifically, the specification defines the term to prevent or treat, i.e. cure, ameliorate, lessen the severity of, or prevent or reduce contagion of infectious disease caused by *B. anthracis*.

(supra). Similarly, specification also describes "treatment of a vertebrate" refers to the use of One or more compositions of the present invention to prevent, cure, retard, or reduce the severity of anthrax disease symptoms in a vertebrate (para 116 of the specification). Therefore, contrary to applicants assertion the term not only embrace a range of outcomes from lessening the severity of the disease to the prevention of infection (see argument page 32, last para. bridging to page 33) but also encompass complete cure from the infection. It is noted "Where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim. Toro Co. v. White Consolidated Industries Inc., 199 F.3d 1295, 1301, 53 USPQ2d 1065, 1069 (Fed. Cir. 1999) (meaning of words used in a claim is not construed in a "lexicographic vacuum, but in the context of the specification and drawings."). Any special meaning assigned to a term "must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention." Multiform Desiccants Inc. v. Medzam Ltd., 133 F.3d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998). See also MPEP § 2111.01. In view of breadth of the definition of term prevention or treatment in the specification, Examiner has analyzed instant claims for prevention and treatment to its full scope. It is emphasized that instant specification is enabling to a method to reduce the severity of anthrax infection in a mammal by administering to the mammal composition of the invention which embrace both aspect of invention to the extent methods retard anthrax infection.

Applicants argument of reducing severity of infection by eliciting effective immune response with 97% identity to SEQ ID No: 4 is persuasive and therefore arguments pertaining to this part of rejection is moot in view of withdrawal of rejection.

To the extent applicant argues a method of preventing anthrax infection by DNA vaccine of the invention, it is emphasized that Examiner agrees that specification teaches a method of reducing the severity of anthrax infection that is encompassed by the term prevention. However, claims directed to prevention are given full breadth as per the specific definition set forth in specification ranging from cure to reducing the severity of infection. Applicant arguments that applicant has shown that immunization of rabbit with VR6292 plasmid has led to the prevention of anthrax infection since the animal survived the anthrax infection (see page 41), animals must have mounted a sufficient immune response not to become ill with lethal dose of anthrax. Applicants assert that it would have been routine optimization for one of skill in the art to test various codon-optimized polynucleotide in mouse, rabbit and primate animal model. Applicant also argues that the post filing reference, co-authored by the inventor, (Ferrari et al., "Development of anthrax DNA vaccines." Curt. Op. in Mol. Therap. 6:506-512, 2004) summarizes various published studies using DNA vaccines formulated with various lipids. Applicant asserts that lipid formulations are not toxic and useful in DNA vaccines. Indeed the Ferrari et al. reference states "there is extensive preclinical evidence suggesting that cationic lipid-based formulations significantly enhance humoral responses of DNA vaccines." Applicants also argue that McCluskie et al cited by examiner shows that many routes actually have been shown to be effective for DNA delivery in mice. (McCluskie et al.,

Molecular Medicine. 5:287-300, (1999) at page 295, and Fig. 1) Applicants also point out that the DNA composition used in McCluskie et al., differ from the instant invention.

In response, it is noted that reference of Ferrari et al also emphasizes the limitations and importance of stability, distribution and ease of administration (see page 508, col. 2, para. 1 and 2). Examiner agrees that a general review of art as well as reference of Ferrari indicates increasing role of cationic lipids in several infectious disease model as shown in table 1. However, it does not provide any evidence that composition comprising (GAP-DMORIE) and any co-lipid administered via any route would elicit immune response to a level sufficient to reduce severity of anthrax infection as exemplified in the instant application. It is emphasized that table 1 merely indicates many different cationic lipid formulations that were used in different infectious disease. In the instant case, the specification as well as post filing art by applicant has exemplified a method that uses carrier comprising DMRIE:DOPE and Vaxfectin (see example and Ferrari et al page 509, col. 2, art of record) that comprises codon optimized PA construct. It is also noted that htPA leader sequence was included in construct for induction of humoral response. The breadth of instant independent claims embrace administering codon optimized plasmid DNA in a carrier comprising DMRIE with any co lipid administered via any route to elicit optimal immune response for the prevention or reduction of severity of anthrax infection. Examiner had cited the reference of Dass to describe various factors that influence lipoflex-mediated nucleic acid transfer *in vivo* that includes type of cationic lipid making up the vesicle, cationic to neutral lipid ratio, and type of neutral lipid in the vesicle (pp 594, col. 1, para 3). Dass et

al conclude that in spite of cationic lipid-DNA complex being the efficient way to deliver nucleic acid into cultured cells. However, it is noted that Dass et al emphasize that their *in vivo* efficacy of lipoflex mediated nucleic acid delivery has shown varying degree of success, primarily due to toxicity associated with these formulations (pp 598, col. 1, last para). It is noted that independent claims 215, 231, 245, 261 and 275 require composition and a carrier comprising GAP-DMORIE and any co lipid. The reference of McCluskie et al cited by examiner is not to show the feasibility of administration of anthrax vaccine rather it is cited to provide general evidence that administration of plasmid DNA in general by different route resulted in varying immune response. It is noted that contrary to applicants argument McCluskie et al also show that administration of DNA vaccine via many non-injectable route of administration such as oral, sub lingual, inhalation and vaginal wall resulted in minimal immune response. Absent of evidence to the contrary, it is not clear that these elements (any co-lipids or any route and sequence with or with leader sequence) would be functional in any mammal in the same manner as it has been exemplified with specific elements that have been demonstrated in the pre clinical model. An artisan would have to perform undue experimentation to empirically test different elements of the composition to specifically adminster in different animal model for eliciting immune response as broadly recited in the instant claims. It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).* It is also well established in case law that the specification must teach those of skill in the art how

to make and how to use the invention as broadly claimed. *In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994)*, citing *In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991)*. An artisan would have to perform undue experimentation to determine the diffewrent elements of the compositions that would elciit immune response in same manner as one exemplified with the speciifc elements set forth in the instant specification.

It is noted that as amedened claims 231 and 261 require new objection as these claims essentially taches same method steps as one disclosed for a method of preventing anthrax infection as set forth in claim 215 and 245 rspectively. Applicant is advised that should claims 231-244, 261-274 be found allowable, claims 215-230 and 245-260 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim.

Claims 215-292 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (US Patent Application no US 2004/0009945, dated 1/15/2004, effective filing date 7/10/1998); Nagata et al (Biochem Biophys Res Commun. 1999, 261(2): 445-51) and Hartikka et al (2001, Vaccine 19:1911-1923) for the reasons of record.

Applicant's arguments, see page 49-50, filed 4/04/2007, with respect to the rejection(s) of claim(s) 215-292 under 35 USC 103(a) have been fully considered and are not fully persuasive. It is noted that applicants cites *In re Kahn* and argues that

obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. Applicant asserts that the Examiner must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention. Applicant also argues that prior arts do not suggest making the specific molecule modification necessary to achieve claimed invention. Applicants further argue that one can conceive a general process in advance for preparing an undefined compound does not mean that a claimed specific compound was precisely envisioned and therefore obvious. Applicant also indicate Nagata do not overcome this deficiency.

In response, it is emphasized that Lee et al taught DNA sequence encoding the protective antigen (PA) from *B. anthracis*. The PA sequence encodes a prokaryotic secretory signal in addition to the entire sequence encoding the 83 Kd PA (SEQ ID NO:1). Lee et al also provided guidance with other nucleic acid sequences wherein the secretory signal has been removed (MAT-PA) or replaced with other secretory signals known to people in the art such as the tissue plasminogen activator (TPA) secretory signal resulting in a DNA fragment encoding TPA-PA (SEQ ID NO:3). Lee et al also disclosed nucleic acid sequences encoding the active form of PA, a 63 kDa protein, termed PA63 (SEQ ID NO:4). It is noted that DNA molecules which comprise a sequence substantially different but due to the degeneracy of the genetic code, still encode the *B. anthracis* proteins as set forth as SEQ ID NO:5 (TPA-PA), SEQ ID NO:6 (PA), SEQ ID NO:7 (MAT-PA)). It is emphasized that Examiner agrees that Lee differed

from claimed invention by not disclosing the codon-optimized sequence as set forth in the instant invention. However, Lee et al clearly suggest that the genetic code and species-specific codon preferences are well known in the art and it would be routine for one of ordinary in the art to generate the degenerate variants described above, to optimize codon expression for a particular host (see entire para 21 of the published application). Nagata taught the codon frequency table that could be used to increases both humoral and cellular immune responses. Lee provided motivation to generate the degenerate variants and it would have required only routine optimization to reach to different codon optimized composition for different mammal as per the breadth of rejected claims. In addition, Lee et al generally embraced the idea of delivering the composition along with a carrier and/or adjuvant by delivering via injection or liposome (see para. 35-37). Furthermore, contrary to applicants argument use of cationic lipid to deliver compositions to elicit immune response was routine in the art. Hartikka et al taught variety of techniques to enhance immune responses against pDNA-encoded antigen including co-injection of pDNA with neutral, anionic and/or cationic lipids. Applicants argument that an artisan would not be motivated to use other antigen since one would not have had an expectation of success in using other antigens because the Hartikka indicated further studies are needed. In response, it is noted that Hartikka stated "experiments are underway to further characterize the Vaxfectin-derived response, and to expand the scope of the application of Vaxfectin adjuvancy for pDNA vaccines to other antigens". It is emphasized that this does not necessarily mean that Vaxfectin would not work with any other antigen. In fact, ongoing experiments with other

antigens could be interpreted as author clearly expected reasonable expectation of success with other antigens. In addition, mechanism by which lipid carrier enhances is not required by any of the pending claims. Lee provided motivation to deliver the composition along with a carrier and/or adjuvant by delivering via injection or liposome. It would have been obvious for one of ordinary skill in the art to deliver the composition comprising sequence disclosed by Lee/ et al. It would be prima facie obvious to one of ordinary skill in the art to further optimize for human codon usage to obtain highly efficient DNA because the prior art suggested that codon optimized DNA preparation is effective with a carrier such as one disclosed by Hartikka. It is noted that prior to instant invention, Lee had already taught a method and composition comprising a nucleic acid encoding protective antigen (PA) protein or its variants from *B. anthracis* in inducing an immune response that is protective against anthrax in subjects. It is emphasized that in absence of any unexpected result, the combined art of Lee, Nagata and Hartikka clearly disclose a sequence that could be codon optimized and delivered via any route to elicit immune response with a reasonable expectation of success.

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